UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

008132

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: EPA ID # 6274-105: DDVP - Review of Metabolism of DDVP in Rats (MRID # 412287-01)

Tox. Chem. No: 328
Project No: 0-0251
Record No: 255872

From: Paul Chin, PhD
Section 2, Toxicology Branch I
Insecticide and Rodenticide Support (IRS)
Hazard Evaluation Division (H7509C)

Paul Chin 10/3/90

To: Jane Talarico, PM 74
Registration Division (H7508C)

Thru: Marion P Copley, DVM, DABT
Head, Section 2, Toxicology Branch I (IRS)
Hazard Evaluation Division (H7509C)

I. CONCLUSIONS:

The Toxicology Branch I has reviewed the metabolism study for DDVP listed in Section II. **ACTION REQUESTED.** Data evaluation records are attached.

The Toxicology Branch I concludes that this study alone does not satisfy the toxicology data requirements for a metabolism study for DDVP in rats (85-1). This study is considered core-supplementary because it is limited to the tissue distribution and excretion of orally administered [^{14}C]DDVP. Additional information on the biotransformation of DDVP (the identification of the urinary and fecal metabolites of DDVP) in rats is required.

II. ACTION REQUESTED:

Review and evaluate the following study:
Metabolism of ^{14}C-DDVP in rats (preliminary and definitive phases). Study No. HLA 6274-105, MRID No. 412287-01, 8/30/89.

III. SUMMARY OF THE EVALUATION OF THE METABOLISM STUDY:

DDVP was readily absorbed from the gastrointestinal tract in groups of five male and five female rats given a single oral dose of 1 or 20 mg [^{14}C]DDVP/kg or a single daily dose of 1 mg unlabeled DDVP/kg for 15 days followed by a single oral dose of 1 mg [^{14}C]DDVP/kg. Approximately 43 to 57 percent of the dose was eliminated in the urine, feces, and expired air (as CO_2) within 24 hours after dosing. Within 7 days, animals eliminated approximately 60 to 77 percent of the radioactive dose in the urine/cage washes, feces, and exhaled air; gastrointestinal absorption was estimated to be between 84 and 93 percent. A large proportion of the administered radioactivity (i.e., 13 to 26 percent) was recovered from the carcass at 7 days after dosing; smaller amounts were found in the liver (3 to 5 percent) and other tissues combined (1 to 2 percent). These data indicate that a considerable amount of radioactivity from [^{14}C]DDVP is retained in the body, even after a single low exposure. Tissue [^{14}C] levels in high-dose animals were proportionately higher than those of low- and repeated-dose animals (i.e., <23 ppm for high-dose rats; <1 ppm for all other animals). For all animals, the liver, kidneys, and bone contained the highest concentrations of radioactivity; the lowest levels were found in the fat. No other marked sex- or dose-related differences in the elimination or distribution of [^{14}C]DDVP were observed. A similar pattern of excretion and tissue retention of radioactivity was observed after intravenous administration of 1 mg [^{14}C]DDVP/kg.

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EPA No.: 68D80056
DYNAMAC No.: 272-A
TASK No.: 2-72A
September 6, 1990

DATA EVALUATION RECORD

DDVP

Metabolism in Rats

STUDY IDENTIFICATION: Cheng, T. Metabolism of ^{14}C-DDVP in rats (preliminary and definitive phases). (Unpublished study No. HLA 6274-105 performed by Hazleton Laboratories America, Inc., Madison, WI, for AMVAC Chemical Corporation, Los Angeles, CA; dated August 30, 1989.) MRID No. 412287-01.

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: William L. McLellan for
Date: Sept 6, 1990

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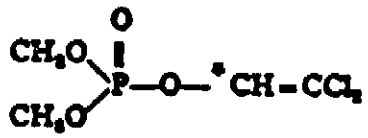
1. CHEMICAL: DDVP; dimethyl dichlorovinyl phosphate.

2. TEST MATERIAL: Unlabeled DDVP (lot No. KB-40-10-4, purity not reported) and [1-^{14}C-vinyl]DDVP (lot No. 2534-039) with a specific activity of 12.9 mCi/mmol and a radiochemical purity of 100 percent were used. The structure and radiolabel position (*) of [^{14}C]DDVP are shown below:



3. STUDY/ACTION TYPE: Metabolism in rats.

4. STUDY IDENTIFICATION: Cheng, T. Metabolism of ^{14}C-DDVP in rats (preliminary and definitive phases). (Unpublished study No. HLA 6274-105 performed by Hazleton Laboratories America, Inc., Madison, WI, for AMVAC Chemical Corporation, Los Angeles, CA; dated August 30, 1989.) MRID No. 412287-01.

5. REVIEWED BY:

Mary E. Cerny, M.S.
Principal Reviewer
Dynamac Corporation

Signature: Mary E Cerny
Date: 9/6/90

William L. McLellan, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: William L McLellan
Date: 9/6/90

6. APPROVED BY:

Nicolas P. Hajjar, Ph.D.
Department Manager
Dynamac Corporation

Signature: Nicolas P. Hajjar
Date: September 6, 1990

Paul Chin, Ph.D.
EPA Reviewer,
Review Section II
Toxicology Branch I
(H-7509C)

Signature: Paul Chin

Date: 9/10/90

Marion Copley, D.V.M.,
D.A.B.T.
EPA Section Head,
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Signature: [illegible]

Date: 10/5/90

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7. **CONCLUSIONS:**

A. DDVP was readily absorbed from the gastrointestinal tract in groups of five male and five female rats given a single oral dose of 1 or 20 mg [^{14}C]DDVP/kg or a single daily dose of 1 mg unlabeled DDVP/kg for 13 days followed by a single oral dose of 1 mg [^{14}C]DDVP/kg. Approximately 43 to 57 percent of the [^{14}C] dose was eliminated in the urine, feces, and expired air (as [^{14}C]CO_2) within 24 hours after dosing. Within 7 days, animals eliminated approximately 60 to 77 percent of the radioactive dose in the urine/cage washes, feces, and exhaled air; gastrointestinal absorption was estimated to be between 84 and 93 percent. A large proportion of the administered radioactivity (i.e., 13 to 26 percent) was recovered from the carcass at 7 days after dosing; smaller amounts were found in the liver (3 to 5 percent) and other tissues combined (1 to 2 percent). These data indicate that a considerable amount of radioactivity from [^{14}C]DDVP is retained in the body, even after a single low exposure. Tissue [^{14}C] levels in high-dose animals were proportionately higher than those of low- and repeated-dose animals (i.e., ≤23 ppm for high-dose rats; <1 ppm for all other animals). For all animals, the liver, kidneys, and bone contained the highest concentrations of radioactivity; the lowest levels were found in the fat. No other marked sex- or dose-related differences in the elimination or distribution of [^{14}C]DDVP were observed. A similar pattern of excretion and tissue retention of radioactivity was observed after intravenous administration of 1 mg [^{14}C]DDVP/kg.

B. This study alone does not satisfy the toxicology data requirements for a metabolism study for DDVP in rats (85-1). This study is considered core-supplementary because it is limited to the tissue distribution and excretion of orally administered [^{14}C]DDVP. Additional information on the biotransformation of DDVP is required.

Items 8 through 10--see footnote 1.

[1]Only the items appropriate to this DER have been included.

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11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods:

1. [^{14}C]DDVP (lot No. 2534-039) was purified before use in the definitive study by thin-layer chromatography (TLC) and subsequent extraction with methylene chloride. The radiochemical purity of the [^{14}C]DDVP used in dosing solutions was determined to be 100 percent by TLC (with a solvent system of benzene:methanol, 20:1, v/v) and gas chromatography (GC).

2. Male and female Crl:CD(SD)BR rats obtained from Charles River Laboratories (Portage, MI) were used. Animals were 5 to 9 weeks old and weighed between 125 and 200 g at the time of arrival at the performing laboratory. The rats were allowed at least 1 week to acclimate before dosing. Animals were fasted overnight to 4 hours postdose.

3. Dosing solutions were prepared on the day of dosing as described below. Measured amounts of purified [^{14}C]DDVP or unlabeled DDVP in methylene chloride were placed in glass vials, and the organic solvent was evaporated under nitrogen; deionized water was added to a final volume, and the mixtures were sonicated to ensure homogeneity. For the high-dose solution only, unlabeled DDVP was used to dilute [^{14}C]DDVP to the final concentration. The [^{14}C]DDVP in the methylene chloride stock solution was found to be stable over the dosing period when examined by TLC and GC (as described in section 11.A.1 of this DER). The [^{14}C] concentration of the radiolabeled dosing solutions was determined by liquid scintillation counting (LSC) before and after compound administration.

4. Twenty-four rats/sex were used. Animals were randomly assigned to the preliminary-phase study or to one of the five groups in the definitive-phase study (Table 1). The two rats/sex in the preliminary-phase study were given a single oral dose of 1 mg [^{14}C]DDVP/kg. In the definitive-phase study, groups of five rats/sex were administered a single intravenous (iv) dose of 1.0 mg [^{14}C]DDVP/kg; a single oral dose of 1.0 or 20.0 mg [^{14}C]DDVP/kg (low- and high-dose groups, respectively); or a single oral dose of 1.0 mg unlabeled DDVP/kg/day for 15 days followed by a single oral dose of 1.0 mg [^{14}C]DDVP/kg (repeated-dose group). Each rat in both the preliminary-phase and definitive-phase studies received 20 μCi of [^{14}C]DDVP. An additional two rats/sex were given a single oral dose of vehicle only (control group). Oral doses were administered by gavage, and iv-administered test material was injected into the tail vein. The dose given to

TABLE 1. Study Design for Animals Dosed with DDVP

Group	Number of Animals/Sex	Target Level (mg/kg)	Actual Dose Level (mg/kg)
Preliminary phase			
Group 1	2	1.0	1.2
Definitive phase			
Group 1 (iv)	5	1.0	1.0
Group 2 (single low oral)	5	1.0	0.8
Group 3 (repeated low oral)[a]	5	1.0	0.8
Group 4 (single high oral)	5	20.0	21.0
Group 5 (control oral)	2	0.0	0.0

[a]Animals were given a single daily dose of unlabeled DDVP for 15 days, followed by a single dose of [^{14}C]DDVP on day 16.

Source: CBI p. 15.

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each animal was determined by weighing syringes before and after dosing.

Rats were placed in individual metabolism cages after administration of radiolabeled DDVP. Animals were checked twice each day for mortality and moribundity and once daily for other signs of toxicity. Body weights were recorded on the first day of treatment, randomly throughout the study, and on study days 7 and 14 (repeated-dose animals). For animals in the preliminary-phase study, urine and feces were collected separately over ice at 0 to 12 and 12 to 24 hours after dosing and daily thereafter for 7 days; for all other animals, urine and feces were collected over ice at 0 to 6, 6 to 12, and 12 to 24 hours postdosing and at 24-hour intervals thereafter for 7 days after compound administration. Expired air (i.e., $[^{14}C]CO_2$) was trapped in a solution of ethanolamine:ethoxyethanol (1:3) at the same time intervals described above. Activated charcoal was used to trap radiolabeled organic volatiles exhaled by animals in the preliminary-phase study only. Cages were rinsed with 1 percent trisodium phosphate at the end of the 7-day collection periods. Animals were sacrificed at 24 hours after dosing (controls) or at 7 days postdosing (all test animals), and the following tissues were collected, weighed, and radioassayed: blood, bone (femur), brain, fat, ovaries/testes, heart, pancreas, liver, kidneys, lungs, muscle (thigh), spleen, uterus, and residual carcass.

5. Aliquots of urine, cage washes/wipes, and CO_2 traps were analyzed directly for $[^{14}C]$ content by LSC. Whole blood samples were combusted and then counted, and feces and all tissues (including the carcasses) were homogenized, combusted, and radioassayed. External standards and an instrument-stored quench curve were used to determine counting efficiencies and to minimize color quenching.

B. Protocol: A protocol for this study is not included in this DER.

12. REPORTED RESULTS:

A. All high-dose rats exhibited tremors and salivation; one female in this group died 2.5 hours after dosing. Several animals in the iv- and repeated-dose groups had dark urine, and one repeated-dose male reportedly consumed no food on days 16 through 20.

B. DDVP was readily absorbed from the gastrointestinal tract of all orally dosed animals. Within 24 hours after dosing, approximately 43 to 57 percent of the [^{14}C] administered was recovered from the urine (8 to 14 percent), feces (2 to 4 percent), and expired air (30 to 41 percent) (Table 2). Within 7 days postdosing, rats had excreted approximately 60 to 77 percent of the radioactive dose in the urine/cage washes (10.5 to 17 percent), feces (4 to 7 percent), and exhaled air (41 to 58 percent) (Table 3). A small sex-related difference in the amount of radioactivity recovered from the exhaled air was observed, with single-dose males (i.e., those given the low or high dose) eliminating slightly less [^{14}C]CO_2 than single-dose females during the 7-day postdosing period (41 to 44.5 versus 52 to 54 percent, respectively). Repeated-dose males and females exhaled relatively similar amounts of [^{14}C]CO_2 (54.5 and 57.5 percent, respectively). Less than 0.1 percent of the radioactivity administered to rats in the preliminary-phase study was trapped by active charcoal as organic volatiles; as a result, the volatiles trap was not used for the other studies. No other differences in the elimination of DDVP were noted. The liver and carcass of all orally dosed animals contained relatively large amounts of radioactivity at 7 days postdosing (3 to 4.5 and 12.5 to 24 percent of the [^{14}C]dose, respectively) (Table 3); in contrast, the remaining 14 tissues combined accounted for only 1 to 1.5 percent of the administered dose. Carcasses of females contained a somewhat smaller amount of radiolabel than carcasses of males (12.5 to 16 versus 20 to 24 percent, respectively). Total recoveries were between 89 and 98 percent for all orally dosed rats.

Similar excretion and tissue/carcass data were reported for iv-dosed animals (Table 4) and for rats in the preliminary-phase study (data not presented in this DER).

C. Individual tissue [^{14}C] concentrations were low (<0.72 ppm) for low- and repeated-dose rats (Table 5). The highest residue levels in these animals were found in the liver (0.495 to 0.717 ppm), kidneys (0.209 to 0.316 ppm), and bone (0.150 to 0.252 ppm); the lowest levels were in the fat (0.038 to 0.054 ppm). Blood and lung [^{14}C] concentrations were 0.125 to 0.150 and 0.132 to 0.186 ppm, respectively. (Tissue [^{14}C] residue levels in iv-dosed animals ranged from 0.05 to 1.0 ppm, with the highest concentrations in the liver, kidneys, and bone, and the lowest levels in fat.)

Radioactivity levels in tissues of high-dose rats were proportionately higher than those in low- and repeated-dose animals and ranged from 1.14 (fat, females) to 23.1 (liver, females) ppm (Table 5). The highest tissue [^{14}C] residues

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TABLE 2. Mean Percent Recoveries of Radioactivity in Urine, Feces, and CO_2 of Rats 24 Hours After Oral Dosing with [^{14}C]DDVP[a]

Fraction	Percent of [^{14}C] Administered to Rats Dosed at: 1 mg/kg		20 mg/kg		Repeated dose[b]	
	Males	Females	Males	Females	Males	Females
Urine	11.86[c]	8.13	12.04	13.87	10.39	11.33
Feces	1.80	3.31	3.23	4.05	2.61	1.99
CO_2	29.50	39.17	33.31	38.76	39.26	41.21
Total	43.16	50.61	48.58	56.68	52.26	54.53

[a]Compiled by the reviewers.

[b]Animals were given a single oral dose of 1 mg unlabeled DDVP/kg for 15 days, followed by a single oral dose of 1 mg [^{14}C]DDVP/kg on day 16.

[c]Each value represents the mean of five animals.

Source: CBI Tables 12-14, 16-18, and 20-22, CBI pp. 39-44, 47-52, and 55-60.

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TABLE 3. Mean Percent Recoveries of Radioactivity in Rats 7 Days after Oral Dosing with [^{14}C]DDVP

Fraction	Percent of [^{14}C] Administered to Rats Dosed at:					
	1 mg/kg		20 mg/kg		Repeated Dose[a]	
	Males	Females	Males	Females	Males	Females
Urine	14.2 ± 1.06[b]	10.4 ± 2.92	14.5 ± 3.41	16.6 ± 1.87	13.1 ± 4.39	14.3 ± 1.41
Feces	4.22 ± 0.861	7.12 ± 2.58	5.87 ± 1.72	6.47 ± 2.74	4.76 ± 3.87	4.86 ± 1.34
Cage wash[c]	0.06 ± 0.057	0.13 ± 0.129	0.17 ± 0.139	0.36 ± 0.591	0.21 ± 0.156	0.07 ± 0.097
CO_2[d]	41.2 ± 3.02	54.0 ± 0.680	44.5 ± 2.06	52.3 ± 3.69	54.5 ± 3.74	57.5 ± 1.92
Liver	3.49 ± 0.195	3.88 ± 0.330	4.42 ± 0.703	4.53 ± 0.429	3.35 ± 0.669	3.74 ± 0.311
Tissues[e]	1.37 ± 0.135	1.33 ± 0.112	1.23 ± 0.173	0.99 ± 0.117	1.41 ± 0.197	1.32 ± 0.181
Carcass	24.1 ± 0.894	16.3 ± 1.23	20.0 ± 3.19	12.5 ± 0.697	20.0 ± 1.43	16.3 ± 0.953
Total	88.7 ± 4.34	93.2 ± 1.06	90.6 ± 4.98	93.5 ± 4.45	97.4 ± 2.79	98.1 ± 1.52

[a]Animals were given a single oral dose of 1 mg unlabeled DDVP/kg/day for 15 days, followed by a single oral dose of 1 mg [^{14}C]DDVP/day on day 16.

[b]Each value represents the mean ± standard deviation of five rats.

[c]Includes cage wipes.

[d]Includes backup CO_2.

[e]Excludes liver and carcass.

Source: CBI Tables 8-12, CBI pp. 34-36.

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TABLE 4. Mean Percent Recoveries of Radioactivity in Rats 7 Days after Intravenous Dosing with [^{14}C]DDVP[a]

Fraction	Percent of [^{14}C] Administered to: Males	Females
Urine	15.4 ± 2.99	12.7 ± 2.40
Feces	4.68 ± 2.62	5.76 ± 2.28
Cage wash[c]	0.18 ± 0.087	0.20 ± 0.079
CO_2[d]	39.5 ± 2.01	50.1 ± 1.50
Liver	4.78 ± 0.652	4.63 ± 0.323
Tissues[e]	1.54 ± 0.273	1.42 ± 0.066
Carcass	26.1 ± 3.04	17.4 ± 1.27
Total	92.2 ± 1.09	92.2 ± 1.83

[a]Animals were given a single intravenous dose of 1 mg/kg.

[b]Each value represents the mean ± standard deviation of five animals.

[c]Includes cage wipe.

[d]Includes backup CO_2.

[e]Excludes liver and carcass.

Source: CBI Table 7, CBI p. 33.

TABLE 5. Mean Concentration of Radioactivity in Tissues of Rats 7 Days after Oral Dosing with [^{14}C]DDVP

Tissue/Organ	[^{14}C]DDVP Equivalents (ppm) for Rats Dosed at: 1 mg/kg		20 mg/kg		Repeated dose[a]	
	Males	Females	Males	Females	Males	Females
Blood	0.130[b]	0.135	3.17	2.95	0.150	0.125
Bone (femur)	0.238	0.150	5.08	2.93	0.252	0.168
Brain	0.053	0.069	1.58	1.77	0.076	0.068
Carcass	0.167	0.133	3.77	2.76	0.171	0.129
Fat	0.044	0.054	1.50	1.14	0.038	0.052
Heart	0.119	0.135	2.75	3.07	0.165	0.144
Kidneys	0.209	0.307	5.27	6.61	0.316	0.295
Liver	0.495	0.717	18.1	23.1	0.710	0.639
Lungs	0.132	0.143	3.52	3.63	0.186	0.154
Muscle (thigh)	0.136	0.082	3.23	1.83	0.097	0.086
Ovaries	NA[c]	0.121	NA	2.72	NA	0.163
Pancreas	0.120	0.135	3.08	2.48	0.185	0.164
Spleen	0.100	0.145	3.35	3.67	0.216	0.185
Testes	0.084	NA	2.19	NA	0.121	NA
Uterus	NA	0.142	NA	4.62	NA	0.234

[a]Animals were given a single oral dose of 1 mg unlabeled DDVP/kg/day for 15 days, followed by a single oral dose of 1 mg [^{14}C]DDVP/kg on day 16.

[b]Each value represents the mean of five animals, except values for high-dose females, which represent the mean of four rats.

[c]Not applicable.

Source: CBI Tables 24-26, CBI pp. 63-68.

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were found in the liver (18.1 to 23.1 ppm), kidneys (5.27 to 6.61 ppm), uterus (4.62), spleen (3.35 to 3.67 ppm), lungs (3.52 to 3.67 ppm), and bone (2.93 to 5.08 ppm); fat had the lowest residue concentrations (1.14 to 1.50 ppm). The mean radioactivity concentration in the blood was 3.17 ppm for males and 2.95 ppm for females.

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The study author reported that 88.7 to 98.1 percent of the [^{14}C]DDVP administered was recovered within 7 days after dosing. The majority of the radioactivity eliminated was recovered as [^{14}C]CO_2 in expired air (39.5 to 57.5 percent of the total dose given to animals in the definitive-phase studies); smaller amounts were found in the urine (10.4 to 16.7 percent) and feces (4.22 to 7.12 percent). Most of the radioactivity in the expired air and excreta (i.e., 43 to 57 percent of the [^{14}C] administered) was eliminated within 24 hours after dosing. Large amounts of radioactivity were absorbed and retained in the carcass (12.5 to 26.1 percent), liver (3.35 to 4.78 percent), and other tissues combined (0.99 to 1.54 percent). The liver, kidneys, and bone generally had the highest [^{14}C] levels and fat had the lowest. The study author concluded that there were no sex- or dose-related differences in the elimination or distribution of [^{14}C]DDVP.

B. A quality assurance statement, signed and dated August 30, 1989, was included in the study.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

This study was conducted adequately according to EPA Guidelines (Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation: Human and Domestic Animals, 1984, Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, DC, pp. 152-156). The selection of dose levels was appropriate, with the low dose corresponding to a no-effect level and the high dose producing some signs of toxicity. Sufficient numbers of animals (five/sex/dose level) were used in each of the definitive-phase experimental groups. The study author's conclusions were supported by the data presented. [^{14}C]DDVP was readily absorbed from the gastrointestinal tract of male and female rats given single low oral, single high oral, or repeated low oral doses of the test material. Within 24 hours after dosing, animals from all groups had eliminated approximately 43 to 57 percent of the [^{14}C] dose in the urine, feces, and exhaled air; within 7 days, approximately 84 to 93 percent of the administered radioactivity was absorbed (based on recoveries from urine, cage

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washes, liver/tissues, CO_2, and carcass; calculated by the reviewers). The majority of [^{14}C] eliminated was recovered as [^{14}C]CO_2 (about 40 to 58 percent of the dose); smaller amounts were found in the urine (10 to 17 percent) and feces (4 to 7 percent). The exhalation of approximately 40 to 50 percent of the radioactive dose as [^{14}C]CO_2 suggests that DDVP is extensively metabolized by rats. However, metabolite profiles were not included in this report, and, thus, additional information on the biotransformation of DDVP was not available. Large proportions of the [^{14}C] doses were retained in the carcass (up to 24 percent for orally dosed rats), liver (3 to 5 percent), and other tissues combined (1 to 2 percent), indicating that radioactivity from [^{14}C]DDVP accumulated in the body even after a single low exposure. Tissue [^{14}C] concentrations were proportionately higher in high-dose rats than in low- and repeated-dose rats, and relatively high levels of radioactivity in the liver (rather than the lungs) suggest that the liver is the primary site for the biotransformation of DDVP. No other significant sex- or dose-related differences in the excretion or distribution of DDVP were reported. Recovery of [^{14}C] was somewhat low (i.e., 88.7 percent) for low-dose males; total recoveries were acceptable (>90 percent) for all other groups. Patterns of [^{14}C] excretion and tissue retention were similar for iv- and orally dosed rats.

Items 15 and 16--see footnote 1.

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END